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October 12, 2005

Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852**SUITABILITY PETITION**

This petition is submitted pursuant to 21 C.F.R § 10.30 and Section 502(j)(2)(c) of the Federal Food, Drug, and Cosmetic Act (Act) to request the Commissioner of Food and Drugs to declare that tretinoin cream drug products in strengths of 0.0375% and 0.075% are suitable for consideration in an Abbreviated New Drug Application (ANDA).

A. Action Requested

The petitioner which holds approved ANDAs for tretinoin cream in strengths of 0.025%, 0.05% and 0.1% requests that the Commissioner of Food and Drugs declare that tretinoin cream in strengths of 0.0375% and 0.075% are suitable for submission in ANDAs. The reference listed drug product on which this petition is based is Retin-A® (tretinoin cream), approved in strengths of 0.025%, 0.05%, and 0.1%. This petition requests a determination of the acceptability of ANDAs for tretinoin cream in the intermediate 0.0375% and 0.075% strengths. The approval of such products would provide increased ability to meet the specific needs of an individual acne patient without presenting any new question pertaining to the safety or effectiveness of tretinoin topical cream therapy in treating acne patients. The drug, dosage form, route of administration, and recommendations for use are the same as those of the listed drug product.

B. Statement of Grounds

The Act provides for the submission of an ANDA for a new drug that differs in dosage strength from that of a listed drug provided that the Food and Drug Administration (FDA) has approved a petition that proposed the filing of such an application. This petition requests authorization to submit ANDAs for dosage strengths of tretinoin cream that differ from that approved for the reference-listed drug.

The proposed 0.0375% and 0.075% dosage strengths would not present any new issues pertaining to safety and effectiveness that are not addressed by the prior approval of the 0.025%, 0.05%, and 0.1% strengths. These new strengths would: (a) be presented in the same dosage form; (b) contain the same active ingredient; (c) have the same route of administration; (d) be intended for the same patient population; and (e) provide the same recommendations for use as the currently approved tretinoin acne products, including the referenced-listed drug, Retin-A®. Further, while the proposed strengths are new, they are bracketed by the currently approved strengths: the 0.0375% strength is

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between the approved 0.025% and 0.05% strengths and the 0.075% is between the approved 0.05% and 0.1% strengths. Current therapy provides for a 2 fold increase in dose between strengths. For many patients, such increases are not tolerated very well. The proposed additional strengths allow for a more gradual increase in drug potency. This should allow for improved patient compliance and tolerance to treatment. Moreover, these new dosage strengths would provide physicians additional flexibility in choosing the appropriate dose for a particular patient, which could have the potential of minimizing side effects and improving tolerability, and thereby increasing the effectiveness, of tretinoin topical therapy in a given patient.

Although topical tretinoin has long been considered standard therapy for acne, it is frequently associated with local reactions, or cutaneous irritation, which can include erythema, edema, peeling, dryness, burning, and itching.¹ Although systemic toxicity has not been linked to topical tretinoin, cutaneous irritation can be somewhat limiting in that it decreases patient compliance.² The development of newer tretinoin products with different formulations and/or vehicles has improved tolerability, but a considerable percentage of patients have remained sensitive to even these formulations.³

Tretinoin-induced irritation has also been shown to be dose-related: the higher the dose, the greater the irritation. For instance, Leyden showed that the retinoid dosage strength significantly impacted tolerability – less erythema was seen with lower concentrations.⁴ Similarly, a photoaging study compared irritation of the 0.1% and 0.025% tretinoin creams. The investigators found a threefold greater incidence of irritation (measured by erythema and scaling) with 0.1% tretinoin.⁵ Cutaneous irritation can decrease patient adherence to treatment with tretinoin, thereby limiting optimal outcomes. Therefore, in selecting a topical treatment for acne, it is important to consider cutaneous irritation and the many factors impacting it, including dosage strength.

Because there are myriad patient differences that prescribing dermatologists must consider when selecting treatment, it is very important for physicians to have access to a variety of topical agents as well as dosage strengths. The new dosage strengths of tretinoin creams proposed (the 0.0375% and 0.075%) will assist prescribing physicians in individualizing acne treatment regimens for optimal therapeutic outcomes. Therefore, petitioner requests that the Commissioner grant this Suitability Petition authorizing the submission of ANDAs for tretinoin creams in the intermediate 0.0375% and 0.075% strengths on the bases that such products would provide increased flexibility in treating acne patients without presenting any approvability issues that could not be adequately addressed through the ANDA process. Indeed, the granting of this Petition would be entirely consistent with the mandates of the Act, as well as FDA's actions on similarly situated Suitability Petitions involving intermediate strengths for a product for which lower and higher strengths were already ANDA eligible.

¹ Lucky AW, Cullen SI, Jarrett MT, Quigley JW. Comparative efficacy and safety of two 0.025% tretinoin gels: results from a multicenter, double blind, parallel study. *J Amer Acad Dermatol*; 1998; 38: S17-23; Phillips TJ. An update on the safety and efficacy of topical retinoids. *Cutis*; 2005; 75 (suppl 2): 14-24.

² Phillips TJ, *supra* note 1.

³ Berson DS, Merchant M. Topical Retinoids in Primary Care Practice. *Medscape*, July 2003; <http://www.medscape.com/viewprogram/2575>, accessed September 2, 2005.

⁴ Leyden J, Grove G, Zerweck C. Facial tolerability of topical retinoid therapy. *J Drugs Dermatol*, 2004; 3:641-51.

⁵ MacGregor JL, Maibach HI. The specificity of retinoid-induced irritation and its role in clinical efficacy. *Exogenous Dermatol*, 2002; 1:68-73.

C. Pediatric Use Information

The Pediatric Research Equity Act, passed in December 2003, requires that applications submitted under Section 505 of the Act be evaluated for safety and efficacy in pediatric populations when the application is submitted for a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration. Because this Petition seeks a change in dosage strength only, it is not necessary to evaluate the safety or efficacy of the product in pediatric populations beyond the currently approved pediatric population or seek a waiver or deferral for pediatric studies.

D. Environmental Impact

This action has no environmental impact and therefore a claim for categorical exclusion is submitted pursuant to 21 C.F.R. Part 25, Subpart C, including section 25.30(h).

E. Economic Impact

Information will be submitted upon request.

F. Certification

The undersigned certify, that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners that are unfavorable to the petition.

Sincerely,

A handwritten signature in black ink, appearing to read "Keith S. Rotenberg", with a stylized flourish at the end.

Keith S. Rotenberg, Ph.D.
Senior Vice President, Regulatory Affairs & Operations